From Network Structure to Dynamics and Back Again: Relating dynamical stability and connection topology in biological complex systems

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The recent discovery of universal principles underlying many complex networks occurring across a wide range of length scales in the biological world has spurred physicists in trying to understand such features using techniques from statistical physics and non-linear dynamics. In this paper, we look at a few examples of biological networks to see how similar questions can come up in very different contexts. We review some of our recent work that looks at how network structure (e.g., its connection topology) can dictate the nature of its dynamics, and conversely, how dynamical considerations constrain the network structure. We also see how networks occurring in nature can evolve to modular configurations as a result of simultaneously trying to satisfy multiple structural and dynamical constraints. The resulting optimal networks possess hubs and have heterogeneous degree distribution similar to those seen in biological systems.

1 Introduction

To see a world in a grain of sand,
And a heaven in a wild flower,
Hold infinity in the palm of your hand,
And eternity in an hour.
– William Blake, *Auguries of Innocence*

Like Blake, physicists look for universal principles that are valid across many different systems, often spanning several length or time scales. While the domain of physical systems has often offered examples of such widely applicable 'laws', biological phenomena tended to be, until quite recently, less fertile in terms of generating similar universalities, with the notable exception of allometric scaling relations [20]. However, this situation has changed with

the study of complex networks emerging into prominence. Such systems comprise a large number of nodes (or elements) linked with each other according to specific connection topologies, and are seen to occur widely across the biological, social and technological worlds [4, 16, 9]. Examples range from the intra-cellular signaling system that consist of different kinds of molecules affecting each other via enzymatic reactions, to the internet composed of servers around the world which exchange enormous quantities of information packets regularly, and food webs which link, via trophic relations, large numbers of inter-dependent species. While the existence of complex networks in various domains had been known for some time, the recent excitement among physicists working on such systems has to do with the discovery of certain universal principles among systems which had hitherto been considered very different from each other.

Reflecting the development of the modern theory of critical phenomena, the rise of physics of complex networks has been driven by the simultaneous occurrence of detailed empirical studies of extremely large networks that were made possible by the advent of affordable high-power computing and the development of statistical mechanics tools to analyze the new network models. Prior to these developments, the networks that were looked at by physicists belonged to either the class of (i) regular networks, defined on geometrical lattices, where each node interacted with all the neighboring nodes belonging to a specified neighborhood, or (ii) random networks, where any pair of nodes had a fixed probability of being linked, i.e., interacting with each other. The first work that focused public attention on the new network approach presented a class of network models that were neither regular nor random, but exhibited properties of both [28]. Such *small world networks*, as they were referred to, exhibited high clustering (with nodes sharing a common neighbor having a higher probability of being connected to each other than to other nodes) and a very low average path length (where the path length between any two nodes is defined as the shortest number of connected nodes one has to go through in order to reach one node starting from the other). As the former property characterized a regular network, while the latter was typical for a random network, this new class of networks was somehow intermediate between the extremes of the two well-known network models, which was manifest in their construction procedure (Fig. 1). Several networks occurring in reality, in particular, the power grid, the actor collaboration network and the neural connection patterns of the *C. elegans* worm, were shown to have the small-world property. Later, other examples have been added to this list, including the network of co-active functional brain areas [1] and the Indian railway system [21].

Very soon afterwards, it was discovered that the frequency distribution of node degree (i.e., the number of links a node has) exhibits a power-law scaling form for a large variety of systems including the world wide web [3]. This further underlined the fact that most networks occurring in reality are neither regular (in which case the degree distribution would be close to a

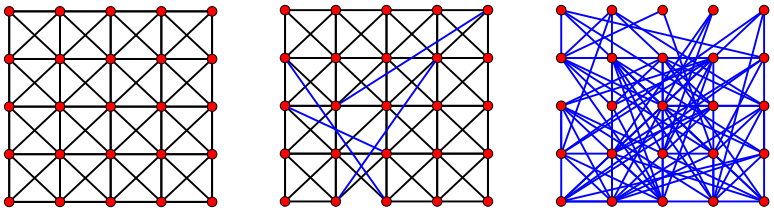

Fig. 1. Constructing a small-world network on a 2-dimensional square lattice substrate. Starting from a regular network (left) where each node is connected to its nearest and next-nearest neighbors, a fraction p of the links are rewired amongst randomly chosen pairs of nodes. When all the links are rewired, i.e., $p = 1$, the system is identical to a random network (right). For small p, the resulting network (center) still retains the local properties of the regular network (e.g., high clustering), while exhibiting global properties of a random network (e.g., short average path length).

delta function) nor random (which has a Poisson degree distribution), as for both cases the probability of having a node with large degree (i.e., a hub) would be significantly smaller than that indicated by the power law tail of empirically obtained degree distributions. In addition, it was observed that there exist non-trivial degree correlations among linked pairs of nodes. For example, a network where nodes with high degree tend to preferentially connect with other high degree nodes, is said to show assortative mixing [15]. On the other hand, in a disassortative network, nodes with large number of links prefer to connect with nodes having low degree. Empirical studies indicate that most biological and technological networks are disassortative, while social networks tend to be assortative [16]. As assortative mixing promotes percolation and makes a network more robust to vertex removal, it maybe hard to understand why natural evolution in the biological world has favored disassortativity. However, in a recent study, we have shown that when one considers the stability of dynamical states of a network, disassortative networks would tend to be more robust, and this may be one of the reasons why they are preferred [6].

This brings us to the thrust of recent work in the area of complex networks which has shifted from the initial focus on purely structural aspects of the connection topology, to the role such features play in determining the dynamical processes defined on a network[27]. Over the past few years, much effort has been made to understand not only how structure affects dynamics, and hence function, in a network, but also the reverse problem of how functional criteria, such as the need for dynamical stability, can constrain the topological properties of a network. In this article, some of the principal results obtained by our group will be briefly described. The goal of our research program is to understand the evolution of robust yet complex biological structures, viz.,

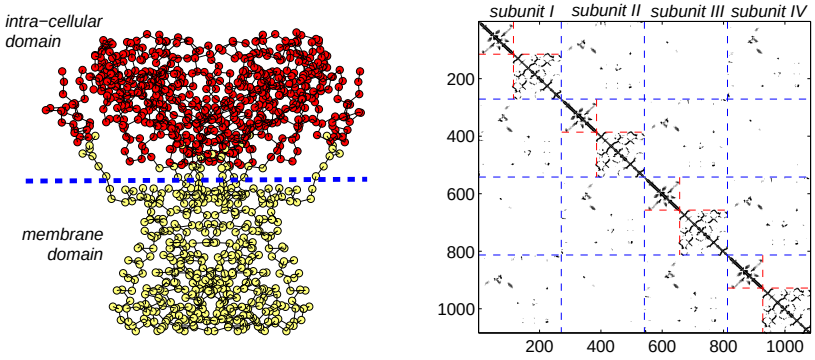

Fig. 2. Structure of the Kirbac1.1 protein (left) which comprises of four identical subunits spanning the membrane and intra-cellular regions [13]. The contact network (PCN) is constructed by considering a cutoff distance of $d_c = 12\mathring{A}$, whose adjacency matrix is shown for the entire network (right). Each of the four blocks corresponding to a sub-unit shows a clear partition into membrane and intra-cellular compartments, indicating a modular structure.

networks occurring in reality that are stable against perturbations and, yet, which can adapt to a changing environment.

2 Biological Networks: Some examples across length scales

Before describing our results that are applicable to a wide range of networks, we provide motivation for our general approach by briefly discussing in this section a few examples of biological networks. Although they span an enormous range of length scales, from $\sim 10^{-8}$ m in the case of protein contact networks to $\sim 10^5$ m in the case of ecological interaction networks, they are often subject to similar constraints and may share common structural and dynamical properties. Questions asked about networks in one domain, may often have answers and ramifications in another domain.

Molecular scale: Protein Contact Network. Protein structure, viewed as a network of non-covalent connections between the constituent amino acids, is one of the smallest length scale networks in the natural world. Its nodes are the C^{α} atoms of each amino acid, and their interaction strength is determined by their proximity to each other. Two nodes are considered to be linked if the Euclidean distance between them (in 3-dimensional space) is less than a cutoff value d_c, usually between 8-14 $\mathring{A}$, which is the relevant distance for non-covalent interactions. Fig 2 shows the Kirbac1.1 protein, belonging to the family of potassium ion channels involved in transmission of inward rectifying

current across a cellular membrane [13]. It consists of four identical sub-units spanning the membrane and intra-cellular regions. The corresponding protein contact network (PCN) manifests the existence of the identical sub-units in the approximately block diagonal structure of the adjacency matrix. In addition, each of these four blocks can be divided into two modules, corresponding approximately to the membrane and intra-cellular regions.

It is easy to see that the PCN shares the features of a small world network, with the majority of connections being between spatially neighboring nodes, although there are a few long-range connections. This small-world property of PCNs for different protein molecules have indeed been noted several times in the literature (see, e.g., Ref. [2]). This is probably not very surprising, given that it is also true for a randomly folded polymer. However, in addition, the PCN adjacency network shows a modular structure, with a majority of connections occurring between nodes belonging to the same module. This is a feature not seen in conventional models of small world networks (e.g., the Watts-Strogatz model [28]). It is all the more intriguing as we have recently shown that modular networks (whatever the connection topology of individual modules) exhibit the small world properties of high clustering and low average path length [18]. To identify whether the existence of modules indeed has a significant effect on protein dynamics (e.g., during folding), we look at the spectral properties of the Laplacian matrix[1] $\mathbf{L}$, defined as $L_{ii} = k_i$, the degree of node i, $L_{ij} = -1$ if nodes i and j are connected, 0 otherwise. The eigenvector for the smallest eigenvalue ($= 0$), $c^{(1)}$, corresponds to the time-invariant properties of the system, and has uniform contribution from all components. The next few smallest eigenvalues dominate the time-dependent behavior of the protein and these show a relatively large spectral gap with the bulk of the eigenvalue spectra. This indicates the existence of very distinct timescales in the protein dynamics which approximately correspond to the inter- and intra-modular modes of motion. As we shall see below, the occurrence of modular structures in complex networks and their effect on dynamics is not just confined to PCNs but appears in many other biological networks.

Intra-cellular scale: Signaling network. Signal transduction pathways, the process through which a cell responds appropriately to a signal or stimulus, involve ordered sequences of biochemical reactions carried out by enzymes inside the cell. One of the most commonly observed class of enzymes in intracellular signaling is that of kinases, which activate target molecules (usually proteins) by transferring phosphate groups from energy donor molecules such as ATP to the targets. This process of phosphorylation is mirrored by the reverse process of deactivation by phosphatases through dephosphorylation. Such reaction cascades are activated by second messengers (e.g., cyclic AMP or calcium ions) and may last for a few minutes, with the number of kinase proteins and other molecules involved in the process increasing with every

[1] The Laplacian is also referred to as the Kirchoff matrix (e.g., see Ref. [10]).

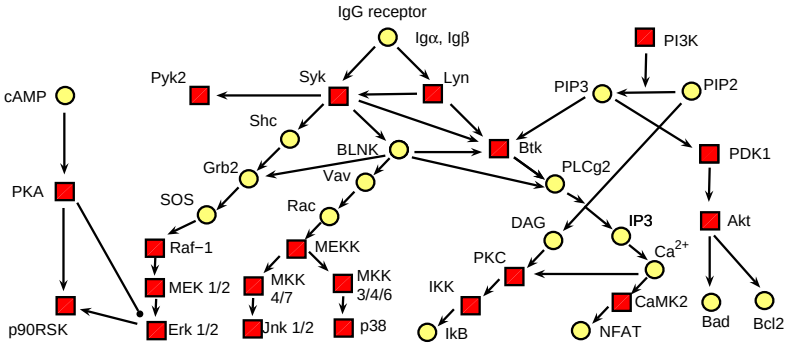

Fig. 3. A subset of the signal transduction network of the B-cell antigen receptor (BCR) [12]. The kinases are represented by squares, while other molecules (such as, second messengers and adapters) are depicted as circles.

reaction step away from the initial stimulation. Thus, such a signalling cascade can result in a large response for a relatively low-amplitude signal.

Research over the past decade has, however, shown that the classical picture of almost isolated cascades linking an unique signal to a specific response does not explain many experimental results. The adaptability of intra-cellular signalling is now thought to be a result of multiple signaling pathways interacting with one another to form complex networks. In this picture, complexity arises from the large number of components, many of which have partially overlapping functions, the large number of links (through enzymatic reactions) among components and from the spatial relationship between the components [29]. Fig. 3 shows a small fraction of the signalling network downstream of the B-cell antigen receptor (BCR) involved in immune response. As the breakdown of communication in this network can lead to disease (a fact that may be utilised by infectious agents for proliferation), it is of obvious importance to understand the mechanisms by which the network allows the cell response to be sensitive to different stimuli and yet robust in the presence of intra-cellular noise. With this in mind, the time evolution of the activity (i.e., phosphorylation) of about 20 signalling molecules in this network were recorded in a recent experiment by Kumar *et al* [12]. Apart from observing the activation profiles under normal conditions, the network was also subjected to a series of perturbations, by serially blocking each of these molecules from activating any of the other molecules in the network. The resulting experimental data, capturing the behavior of these molecules under 21 different conditions, enabled the detection of correlations between the activity of these molecules. This showed that the existing picture of interactions (Fig. 3) is grossly inadequate in explaining these correlations, e.g., the fact that p38 kinase seems to influence the activation of a majority of the other molecules, although it occurs at the end of particular pathway. The results suggest that the signalling

network is in fact a far more densely connected system than had been previously suspected. It also raises the question of how certain signals can elicit very specific responses, without significant risk of cross-talk between interacting pathways. This brings us to the issue of whether functional modules can exist in networks, such that by using positive and negative interactions one can channel information from the stimulus to the response along specific subnetworks only.

Inter-cellular scale: Neuronal Network. The above question is of importance not only for information processing within a cell, but also between cells. The most important example of the latter process is, of course, the networks of neurons occurring in the brain. As the nervous system of the nematode *C. elegans* comprising 302 neurons has been completely mapped out (in terms of the positions of the neurons, as well as all their interconnections), it provides a model system for studying these issues. We have recently analysed the connection topology of the non-pharyngeal portion of the nervous system to which the majority of the neurons ($\simeq$ 280) belong [7]. One of the striking observations is that many of the sensory neurons belonging to different modalities, viz. chemosensation, mechanosensation, etc., send signals to the same set of densely connected interneurons which forms the innermost core of the nervous system. Subsequently, signals are sent from these interneurons to specific motor neurons which generate appropriate muscle response, e.g. moving along a chemical gradient, egg-laying. etc. It is vital that the signals coming from different sensory neurons to the same interneurons should not interfere with each other, as it may result in activating the incorrect motor response. A preliminary investigation of a dynamical model for the neuronal network shows that, a complex set of excitatory and inhibitory links between the inter-neurons manages to achieve segregation of the different functional circuits. This means that, e.g., a mechanical tap signal will not elicit egg-laying, even if the tap withdrawal circuit may share many common interneurons with the egg-laying circuit. Even more interesting is the fact that such functional modules do not need the existence of structural modules in the underlying networks. It underscores the importance of looking at the nature of the interactions, which can create complicated control mechanisms to prevent cross-talk and enable robust response in the presence of environmental noise.

Inter-organism scale: Epidemic Propagation Network. At the scale of individual organisms, such as human beings, one of the most widely studied networks is that which leads to propagation of epidemics. The ubiquity of small-world networks in nature implies that some of the classic theories of epidemiological transmission, based on assumptions of random connections, may need to be reviewed. In particular, the global spread of diseases like SARS shows that even a few long-range links can drastically enhance the propagation of epidemics [8]. This has led to a series of studies of different disease propagation models on Watts-Strogatz (WS) or related network models (e.g.,

see Ref. [19]). However, as mentioned above, all the structural features of such networks are also shared by modular networks, which however have very different dynamical properties. We have recently shown that while WS networks have a continuous range of time-scales, modular networks exhibit very distinct time-scales that are related to intra- and inter-modular events [18]. Thus, devising an effective strategy to counter the spread of epidemics will have to take into account a detailed knowledge of such structures in the social network of contagious and susceptible individuals.

Inter-species scale: Food Webs. Possibly the largest (in terms of length scale) biological networks on earth are those of interactions between different species in an ecosystem. While general ecological networks consist of all possible links, such as cooperation and competition, food webs describe the trophic relations, i.e., between predator and prey. It is a directed network where the nodes are the various species, with prey connected by arrows to predators, the direction of the arrow indicating the flow of biomass. The links are usually weighted to represent the amount of energy that is transferred. It is in the context of these networks that questions first arose on the connection between the structural properties of a network and the stability of its dynamical behavior (see Sec. 4). Indeed, one can not only ask what kind of structures allow complex networks to be stable against ever-present perturbations, but also, how the requirement to be robust constrains the kind of structures such networks can evolve. To stress the universality of the questions asked by physicists about networks, we note that like many other networks, food webs also have been shown to have modular structure, with species in each module interacting between themselves strongly and only weakly with other species [11]. As in the other systems discussed earlier, the role that modularity plays in stabilizing the dynamics of ecosystems can be seen as a specific instance of a much more general question.

Having discussed a few instances of how universal principles about networks can appear by investigating very different systems in the biological world, we now describe certain results of our studies on general network models. However, we stress that each of these results have relevance to problems appearing in the context of specific biological systems.

3 From Structure to Dynamics

The role that the connection topology of a network plays in the nature of its dynamics has been extensively investigated for spin models occurring in physics. In fact, such systems had been explored for a long time prior to the recent interest in complex networks, and many results are known regarding ordering transition in both regular as well as random structures. More recently, it has been shown that, for partial random rewiring in a system of sufficiently large size, any finite value of p (the rewiring probability) causes a transition to the small-world regime, with the Ising model defined on such a network

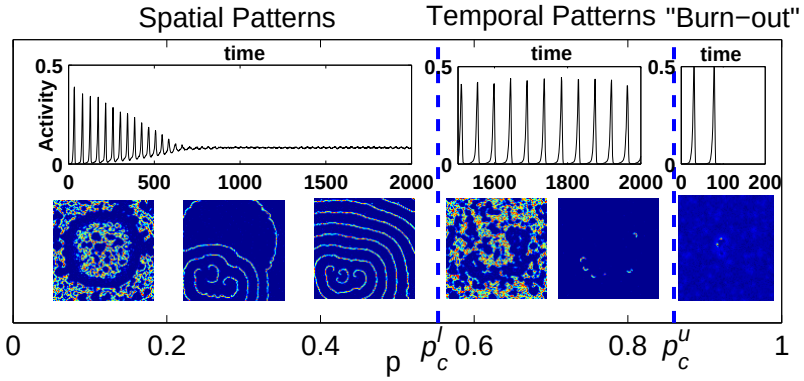

Fig. 4. Schematic diagram indicating the different dynamical regimes in a two-dimensional "small-world" excitable medium as a function of the rewiring probability, p. For low p, the system exhibits spatial patterns characterized by single or multiple spirals. At $p = p_c^l$, there is transition to a state dominated by temporally periodic patterns that are spatially relatively homogeneous. Above $p = p_c^u$, all activity ceases after a brief transient.

exhibiting a finite temperature ferromagnetic phase transition [5]. However, spin models are extremely restricted in their dynamical repertoire and therefore, researchers have looked at the effect of introducing other kinds of node dynamics in such network structures, e.g., oscillators. Motivated by recent observations that the brain may have a connection structure with small-world properties (see e.g., Ref. [1]), we have examined the effect of long range connections (i.e., non-local diffusion) over an otherwise regular network of nodes with links between nearest neighbors on a square lattice [25]. The dynamics considered is that of the excitable type, with the variable having a single stable state and a threshold. If a perturbation causes the system variable to exceed the threshold, we see a rapid transition to a metastable excited state followed by a slow recovery phase when the system gradually converges to the stable state. As a result of coupling the dynamics of individual nodes through diffusive coupling, various spatial patterns (which may be temporally varying) are observed. Such dynamics is commonly observed in a large variety of biological cells such as neurons and cardiac myocytes, as well as in nonlinear chemical systems such the Belusov- Zhabotinsky reaction.

In our simulations, by varying the probability of long-range connections, p, we have observed three categories of patterns. For $0 < p < p_c^l$, after an initial transient period where multiple coexisting circular waves are observed, the system is eventually spanned by a single or multiple rotating spiral waves whose temporal behavior is characterized by a flat power spectral density. At $p = p_c^l$, the system undergoes a transition from a regime with temporally irregular, spatial patterns to one with spatially homogeneous, temporally periodic patterns (Fig. 4). The latter behavior occurs over the range $p_c^l < p < p_c^u$

as a result of the increased number of long range connections, whereby a large fraction of the system gets synchronously active and subsequently goes into the recovery phase. Beyond the upper critical value p_c^u, there is no longer any self-sustained activity in the system as all nodes converge to the stable state. The patterns in each regime were found to be extremely robust against even large perturbations or disorder in the system.

Our model explains several hitherto unexplained observations in experimental systems where non-local diffusion had been implemented [26]. In addition, by identifying the long-range connections with those made by neurons and the regular network with that formed by the glial cells in the brain, our results provide a possible explanation of why evolution may have preferred to increase the number of glial cells over neurons (with a ratio of more than 10:1 for certain parts of the human brain) in order to maintain robust dynamical patterns as brain size increased. It also points towards possible functional role of small-world brain topology in the occurrence of dynamical diseases such as epileptic seizures and bursts. More generally, our work shows how non-standard network topologies can influence system dynamics by generating different kinds of spatiotemporal patterns depending on the extent of nonlocal diffusion.

4 From Dynamics to Structure

An important functional criterion for most networks occurring in nature and society is the stability of their dynamical states. While earlier studies have concentrated on the robustness of the network when subjected to structural perturbations (e.g., removal of node or link), we have looked at the effect of perturbations given to the steady states of network dynamics. In particular, the question we ask is whether networks become more susceptible to small perturbations as their size (i.e., number of nodes N) increases, the connections between the nodes become denser (i.e., increased connectance probability C) and the average strength of interaction (s) increases. This is related to a decades-old controversy, often referred to as the stability-complexity debate. In the early 1970s, May [14] had shown that for a model ecological network, where species are assumed to interact with a randomly chosen subset of all other species, an arbitrarily chosen equilibrium state of the system becomes unstable if any of the parameters determining the network's complexity (e.g., N, C or s) is increased. In fact, by using certain results of random matrix theory, the critical condition for the stability of the network was shown to be $NCs^2 < 1$ (May-Wigner theorem) [14]. This flew against common wisdom, gleaned from large number of empirical studies as well as naive reasoning, which dictated that increased diversity and/or stronger interactions between species results in more robust ecosystems. Thus, ever since the publication of these results, there have been attempts to understand the reason behind the apparent paradox, especially as this result relates not only to ecological systems but extends to all dynamical networks for which the stability of

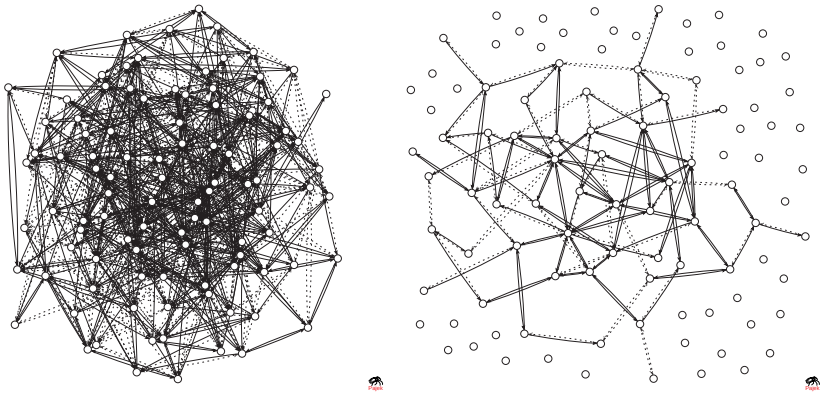

Fig. 5. Evolution of a network with non-trivial dynamics at the nodes. The initial (left) and final asymptotic (right) networks are shown. Only nodes having persistent activity are connected to the network. The figures were drawn using Pajek software.

equilibria have functional significance, e.g., in intra-cellular biochemical networks where the concentrations of different molecules need to be maintained within physiological levels. Two of the common charges leveled against the theoretical model of May is that (i) it assumes the interaction network to be random whereas naturally occurring networks may have certain kinds of structures, and (ii) the linear stability analysis assumes the existence of simple steady states (viz., fixed point attractors), which may not be the case for real systems that may either be having oscillations or be in a chaotic state.

In our work on dynamical systems defined on networks, we have tried to address both of these lines of criticism (see Ref. [31] for a recent discussion of our results from the perspective of ecosystem robustness). For example, focusing on the question of inadequacy of linear stability analysis, we have considered networks with nontrivial dynamics at the nodes, spanning the range from simple steady states to periodic oscillation and fully developed chaos, and measured the robustness of the dynamics with respect to variations in N, C and s [23, 24].

Each node in our model network has a dynamical variable associated with it, which evolves according to a well-known class of difference equations commonly used for modeling population dynamics. By varying a nonlinear parameter, the nature of the dynamics (i.e., whether it converges to a steady state or undergoes chaotic fluctuations) at each node can be controlled. However, in the absence of coupling, each node will always have a finite, positive value for its dynamical variable. When coupled in a network (initially in a random fashion), with links that can have either positive or negative weights, it is possible that as a result of dynamical fluctuations, the variable for some nodes can become negative or zero. As this implies the absence of any activity, the corresponding node is considered to be "extinct" and thus isolated from

the network. This procedure may create further fluctuations and cause more nodes to get "extinct", resulting in gradual reduction of the size of the network (Fig. 5). The final asymptotic size of the network, relative to its initial size, is a measure of its robustness - the more robust network being one with a higher fraction of nodes having persistent activity. Analysis showed that the network robustness (as measured by the above global criterion) not only decreased with N, C and s, as expected from local stability analysis, but actually matched the May-Wigner theorem quantitatively [23]. In addition, the asymptotic network exhibited robust macroscopic features: (a) the number of persistently active nodes was independent of the initial network size, and (b) the asymptotic number of links between these persistently active nodes was independent of both the initial size and connectivity [24]. This is all the more surprising as the removal of nodes (and hence, links) is not guided by any explicit fitness criterion but rather emerges naturally from the nodal dynamics through fluctuations of individual node properties. Our results imply that asymptotically active networks are non-extensive: when two networks of size N are coupled to each other (with the same connectance as the individual networks), although the resulting network initially has a size $2N$, the ensuing dynamical fluctuations will reduce its size to N. This implies that simply increasing the number of redundant elements is not a good strategy for designing robust systems.

We have also looked at the effect of empirically reported structures, such as small-world connection topology and scale-free degree distribution, on the dynamical stability of networks. Our results indicate that, in general, introducing such structural features do not alter the outcome expected from the May-Wigner theorem [6, 22]. However, these details can indeed affect the nature of the stability-instability transition, for example, the transition exhibiting a cross-over from being very sharp (resembling first-order phase transition) for a random network to a more gradual change as the network becomes more regular in the small world regime [22].

5 Evolution of Robust Networks

This brings us to the issue of how complex networks can be stable at all, given that the May-Wigner theorem seems to hold even for networks that have structures similar to those seen in reality and where non-trivial dynamical situations have also been considered. The solution to this apparent paradox lies in the observation that most networks that we see around us did not occur fully formed but emerged through a process of gradual evolution, where stability with respect to dynamical fluctuations is likely to be one of the key criteria for survival. In earlier work, we have shown that a simple model where nodes are gradually added to or removed from a network according to whether this results in a dynamically stable network or not, results in a non-equilibrium steady state where the network is extremely robust [30]. The

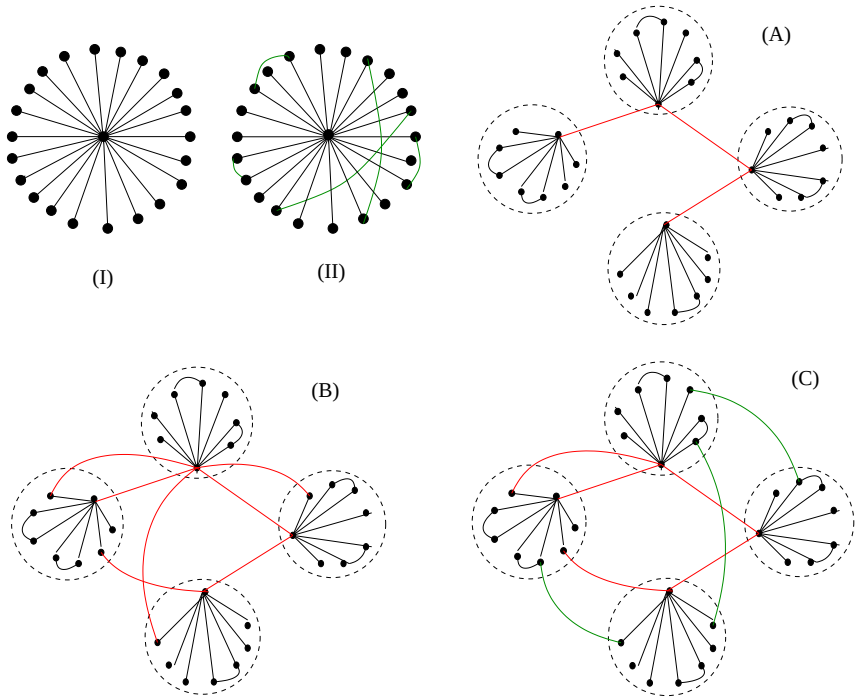

Fig. 6. Networks with (I) star and (II) clustered star connection topology, can form the fundamental building blocks of different types of modular networks. Network configurations having clustered star modules can be constructed by (A) connecting different modules by single undirected links among the hub nodes, or (B) connecting nodes of a module to another module only through the hub node of the latter, or (C) connecting nodes of a module randomly to any node of another module.

robustness is manifested by increased resistance and resilience, as well as, decreased probability of large extinction cascades, when the network size (i.e., the system diversity) is increased. Thus, our results reconcile the apparently contradictory conclusions of the May-Wigner theorem and a large number of empirical studies.

More recently, we have shown that model networks can evolve many of the observed structural features seen among networks in the natural world, by taking into account the fact that most such systems have to optimize between several (often conflicting) constraints, which may be structural as well as dynamical in nature. In particular, most networks need to have high communication efficiency (i.e., low average path length) and low connectivity (to reduce the resource cost involved in maintaining many links) while being stable with respect to dynamical perturbations. If a network satisfied only the first two constraints, the optimal structure would have been that of a star (Fig. 6). Even if the resource cost constraint is somewhat relaxed, so that the network

can have more links than the minimum necessary to make it connected, the resulting optimal configuration is slightly modified to that of a "clustered" star. However, we note that the dynamical equilibria in such systems would be extremely unstable with respect to small perturbations. This is because the rate of growth of small perturbations is related to the maximum degree of the network, which, in the case of a star or a clustered star, is almost identical to the system size. It is easy to see that dividing the network into multiple stars, connected to each other, will reduce the maximum degree and hence increase the stability. Indeed, our results show that simultaneous optimization of all three constraints result in networks with modular structure, i.e., subnetworks with a high density of connections within themselves compared to between distinct subnetworks, where each module possesses a prominent hub [17] (see Fig. 6 for possible configurations of such modular networks). As these evolved systems also exhibit heterogeneous degree distribution, our findings have implications for a wide range of systems in the biological and technological worlds where such features have been observed.

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